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MEDICAL REVIEW

Origins of Cancer Therapy

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This is a brief overview of the development of cancer therapy with a focus on systemic therapy. The modern era of chemotherapy developed at Yale University Medical School during World War II, a fact that has been generally unrecognized until recently. The observations preceding and involved in the discovery of effective drugs for cancer seem particularly pertinent for this anniversary year.

While the modern era of cancer chemotherapy began following the World War II, the origins of cancer treatment are recorded in ancient documents. Although most treatments for advanced cancer were ineffective until the nineteenth century, it is of interest to review some pertinent examples of the volution of cancer therapy.

The Ebers papyrus, the Edwin Smith papyrus, and the Ramayana describe malignant diseases and their treatments [1-3]. Most frequently, therapy consisted of topical preparations although removal of neoplasms had been practiced in antiquity [2]. Mastectomy was described during the Roman period by Celsus and Leonides [4].

Dioscorides, in the first century A.D., compiled a listing of medicinal herbs and botanicals, including topical applications for treatment of tumors and carcinomata [5]. These treatments were in use for 15 centuries [6].

In the eleventh century an Arabic physician, Ibn Sina, known in the West as Avicenna, used arsenical therapy systemically, although it was found to be dangerous and received little attention [7]. Arsenical preparations known as *Unguentum Aegypticum* were used topically until the sixteenth century [6].

Many consider the use of potassium arsenite to treat chronic myelogenous leukemia in 1865 by Lissauer as the first instance of effective chemotherapy for malignant disease [8]. The patient improved, but no blood counts were obtained, and it was only after 13 years that the beneficial effects on the peripheral blood were reported [9]. The use of arsenicals (Fowler's solution) to treat leukemias continued until the 1930s [10]. The past decade has witnessed a return to

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the use of arsenical therapy, such as arsenic trioxide, which is now established as a very effective treatment for acute promyelocytic leukemia [11, 12].

Radiation therapy was undoubtedly the most effective form of antitumor treatment besides surgery for almost the first half of the twentieth century. Following Roentgen's discovery of x-rays, radiation therapy developed rapidly, although the methodology was primitive as compared to present day standards [13]. In the United States, Pusey and Senn reported results in treatment of lymphomas and leukemia in 1902 and 1903 [14, 15]. In some instances, the results were dramatic and suggested cures, although the development of relapse of disease and complications of treatment quickly altered the initial optimism.

Within a year of Roentgen's publication regarding the discovery of x-rays, another report of effective antitumor therapy appeared. Beatson, writing in the Lancet in 1896, noted benefit following oophorectomy in three patients with inoperable carcinoma of the breast [16]. The rationale for the use of oophorectomy was not because of any known hormonal effects recognized at that time. Hormonal mechanisms were, however, elucidated almost 50 years later when the role of androgens in prostate cancer was described by Huggins [17].

Over the centuries, numerous nostrums were tried for systemic neoplastic disease. In 1767, Burrows (*A New Practical Essay on Cancers*, London) summarized, "that whatever has been proposed for the curing of cancers, are merely palliative medicines; and that no real specific has been hitherto discovered for that fatal disorder, although the physicians of all nations, from the time of Hippocrates to the present, have, by numberless researches and experiments, made trial of every thing in nature, from the most innocent drug, to the most virulent poison, both in the mineral and vegetable kingdoms; yet the disease still baffles the power of physic" [18]. Similar views are stated in 1914 when Bainbridge wrote, "Throughout the centuries, the sufferers of this disease have been the subject of almost every conceivable form of experimentation. The fields and forests, the apothecary shop and temple have been ransacked for some successful means of relief from the intractable malady. Hardly any animal had escaped making its contribution to hide or hair, tooth or toenail, thymus or thyroid, liver or spleen, in the vain search for a means of relief" [19].

Late in the nineteenth century a surgeon, William Coley, developed a mixture of bacterial toxins known as Coley's toxin which induced regression of some tumors [20]. Other sera and bacterial toxins were developed, since one theory of the causation of cancer was the concept of some unidentified organism as a causative agent [21].

Other therapeutic measures included blood transfusions, splenectomy, thyroidectomy, oxygen therapy, fever therapy, pituitary extract, and the use of organ extracts such as extracts of animal spleen, bone marrow, lymph nodes, pancreas, stomach, and small intestine [19]. Vitamins and minerals were also administered. Starvation diets were recommended by some physicians on the basis of the observation of cachexia in cancer patients, considered to be beneficial by depriving the tumor of nutritional needs [22].

The lack of effective treatment did not deter claims for treatment benefits. Bryant, writing in the *Boston Medical and Surgical Journal* (1921), stated, "decided advances have been made in the past fifteen years and cancer may now be considered a somewhat preventable, somewhat curable disease" [23]. In 1920, however, in an editorial in the *Canadian Practitioner and Review*, the author commented on publicity arising from the use of an anti-

cancer serum, "the newspapers are full of the most objectionable items published in wholesale style, such as "cancer patients are markedly better" and "all are improved." From the standpoint of the patients alone, this is unadvisable, if not absolutely cruel" [24].

However, during the 1920s and 1930s an important advance that aided in the development of the modern era of cancer treatment was the development of animal systems that were to be predictive for antitumor drugs [25-27]. These systems laid the groundwork for subsequent drug screening programs.

The origins of effective chemotherapy for cancer date to World War I when mustard gas (sulfur mustard) was used. The blood and bone marrow findings in cases of mustard gas poisoning were described by Krumbhaar and later by Krumbhaar and Krumbhaar in 1919 [28, 29]. The time sequence of marrow depression revealed a maximal effect at two weeks after exposure when mortality was highest. Deaths were attributed in some cases to pneumonia associated with leucopenia. Autopsies revealed atrophy of lymphoid and testicular tissue as well as hypoplasia of the bone marrow.

In 1929, Berenblum, in studying carcinogenesis, observed that sulfur mustard was "anti-carcinogenic" [30]. In attempting to enhance the development of tumors induced by a carcinogenic tar, Berenblum and Riley-Smith added a solution of mustard gas, assuming that the local irritant effect of the mustard gas would induce hyperemia that was beneficial to tumor development. As described by the authors, the result was diametrically opposite. The mustard gas application inhibited the induction of tumors, and further experiments suggested that this was mediated by an effect of mustard gas on the animal rather than some interaction with the carcinogenic substance. Berenblum and Riley-Smith continued to investigate the "anticarcinogenic" effects of mustard gas, observing that inhibition of tumors induced by other carcinogens such as dibenzanthracene also occurred with mustard gas [31]. Other topical irritants were studied for tumor inhibition, and the only other agent not closely related to mustard gas with some tumor inhibitory activity was noted to be cantharidin.

Recognition of the possible importance of sulfur mustards in cancer research was later cited. Dr. James Ewing at the Memorial Hospital in New York recommended the study of the effects of mustard gas on experimental tumors, reported in 1931 [32]. Adair and Bagg applied a solution of mustard gas to the skin of normal mice and to a tumor induced by a chemical carcinogen [32]. Tumor regression was evident in the cutaneous tumor although autopsy showed a metastatic lung nodule in the animal. Varying doses of mustard gas application to the skin of the rabbit were assessed to determine appropriate doses for local use. This was followed by the application of topical mustard gas to cutaneous lesions of twelve patients and intratumoral injection in one individual at the Memorial Hospital in New York and reported by Adair and Bagg in 1931. The results included a "violent therapeutic reaction" and virtual disappearance of tumor after the intratumoral injection. The tumors studied included melanoma, squamous cell carcinoma of the skin, neurofibroma, neurogenic sarcoma and two cases of penile carcinoma.

All showed regression for a period of months: there was no long-term follow up reported, and a cautionary statement warned that intratumoral injection required care since destruction of vital parts could ensue. The authors concluded that mustard gas solution represented another agent for treatment of localized cancer.

Despite this work, which is seldom cited, it was well over a decade before

alkylating agent therapy was introduced into clinical use. Topical use of the nitrogen mustards was not practiced until 1956 when it was found to be useful for mycosis fungoides [33].

The advent of World War II stimulated further research on chemical warfare. A series of analogues of sulfur mustards were produced as potential offensive agents. It was recognized that beta chlorethyl amines could exert cytotoxic actions on a variety of tissues, particularly related to the degree of their proliferative activity. Further study of the basic mechanisms of cellular effects of the sulfur and nitrogen mustards suggested that their effects resembled those of x-rays.

Since the data were classified during wartime, these findings were reported following World War II by Goodman and Philips from the Pharmacology Section, Medical Division of the Chemical Warfare Service of the U.S. Army [34]. It was suggested that the clinical application to neoplastic disease was possible. In fact, in 1942, Gilman, Goodman, Philips, and Allen at Yale discovered the antitumor activity of nitrogen mustard (methyl-bis) (beta-chlorethyl) (amine hydrochloride) [35]. The use of these compounds was restricted due to war time secrecy; hence the publication was delayed until 1946.

Interestingly, major textbooks of cancer medicine have erroneously attributed the initial use of nitrogen mustard to findings of exposure to mustard gas following an explosion that occurred in Bari Harbor in 1943 [36, 37]. The initial clinical trial occurred at Yale in May 1942 [35].

The initial clinical trial of nitrogen mustard was reviewed by Gilman almost 20 years later [35]. He stressed that prior to clinical trial there were thorough animal studies conducted. Pharmacologic studies of the nitrogen mustard in rabbits revealed a remarkable sensitivity of lymphoid tissues to cytotoxic action of the nitrogen mustards.

It seemed natural, therefore, to examine the susceptibility of lymphoma to the nitrogen mustards. Gilman, Goodman, and Philips who had made the observations in rabbits turned to Thomas Dougherty, an anatomist, who first studied the compounds in mice, to ascertain the lethal dose and bone marrow effects. Doughtery, who was working with Gardner on a transplanted lymphoma, originally from an estrogen treated mouse, ultimately known as the Gardner lymphosarcoma, tried nitrogen mustard in a mouse with an advanced tumor. The tumor began to regress after two injections and became impalpable. The tumor recurred and was successfully treated although there was less regression than noted with the initial treatment. The animal, whose survival with this type of tumor was generally three weeks, survived for 84 days.

The observation was followed by testing in several other animal lymphomas and leukemias. None demonstrated the striking effect noted in the Gardner lymphosarcoma, and in some the treatment was completely ineffective. Gilman later wrote, "I have often thought that if we had by accident chosen one of these leukemias, in which there was absolutely no therapeutic effect, we might possibly have dropped the whole project" [34]. This serendipitous choice was paralleled in the human trial that followed.

In May 1942, a therapeutic trial in man was carried out under the supervision of Dr. Gustav E. Lindskog, an Assistant Professor of Surgery. The patient was described as "an x-ray resistant patient in the terminal stages of lymphosarcoma." The patient was a man, aged 48, who had received radiation therapy in March 1941 with considerable reduction in tumor involving the right tonsil, cervical nodes and axilla as well as mediastinum. In December 1941, he had recurrent disease treated by radiation therapy. In May 1942, he again received radiation therapy to treat

the disease which now was associated with neck and facial edema, venous dilatation of the upper chest, and inability to adduct his arms due to large axillary masses. During this treatment, the patient did not respond to the radiation, so ten consecutive daily doses of nitrogen mustard 0.1 mg/kg were administered daily for 10 days.

On the fourth day of therapy, improvement was noted and by the last day of treatment, all signs and symptoms of his disease were gone. The response of the patient was striking and very much like the observations in the animal tumor.

The patient relapsed after one month, was then treated with a lesser dose (he experienced severe leuconeutropenia after the initial treatment) as well as thrombopenia (22,000 platelets/mm^3) and some cutaneous purpura. He received a third course three weeks later to which he did not respond.

These observations generated considerable excitement and were followed by treatment of several patients who were in the terminal stages of malignant disease in a variety of tumors. Early reports documented some dramatic responses in Hodgkin's disease patients who had become refractory to radiation therapy. An example is the case of a 33-year-old woman who presented with dyspnea, cough, motor and sensory paresis of the right arm, and adenopathy of the axilla, neck and mediastinum. The patient also had edema of the breasts, and fevers to 103°F. Following four doses of nitrogen mustard at 0.1 mg/kg, improvement developed with disappearance of fever, dyspnea, and cough. The edema of her arms and breasts receded completely with 75 percent reduction in adenopathy.

As in the animal experiments, some tumors were resistant to the treatment. The clinical results in the acute leukemias were disappointing. No benefit was noted in melanoma, cervical carcinoma, and some lymphoma patients.

As expected from the animal data, bone marrow depression was a major toxic effect of the treatment. In the animal studies, the bone marrow suppression was reversible, and a fairly wide margin existed between marrow suppressive and lethal doses. As noted, the initial human dose was 0.1 mg/kg daily for 10 days. At three weeks following treatment, the total white count was 200 cu/mm and severe thrombopenia was noted. In man, the marrow recovery was prolonged in some instances, so dose modifications were utilized. The standard dose evolved to 0.1 mg/kg for four days.

It is noteworthy that Wilkinson and Fletcher in England began independent clinical trials with nitrogen mustards in 1942 but did not publish the data until 1947 [38], citing the restrictions of secrecy during the war. From their report it is unclear what constituted the stimulus for a clinical trial apart from a similarity of the hematopoietic effects to those produced by x-rays. Eighteen patients were treated including eight with chronic myelogenous leukemia, three with chronic lymphocytic leukemia, four with Hodgkin's disease, and three with polycythemia vera. The tris compound was utilized rather than the bis compound used in the American studies. The doses applied were smaller than those used at Yale. The most striking benefit was noted in chronic myelogenous leukemia, although significant benefit was observed in Hodgkin's disease.

Between 1943 and 1946 clinical studies with nitrogen mustard were extended to include Leon Jacobson in Chicago, Maxwell Wintrobe at Salt Lake City, William Dameshek in Boston, and Cornelius Rhoads and David Karnofsky in New York [39-41]. In 1946, C.P. Rhoads who was chairman of the Committee on Growth of the National Research Council reported the findings in the Journal of the

American Medical Association [42]. The conclusion was that the nitrogen mustards were not a cure for neoplastic diseases and the tumor regressions were temporary. It was suggested that laboratory and clinical studies should continue in the hope that certain types of cancer might prove to be unusually sensitive to these agents and that compounds with more selective action on cancer tissue might be discovered.

During the period of the development of nitrogen mustards, the era of effective antibiotic therapy for infectious diseases began. By analogy, some investigators believed that one agent could be developed to cure turmors — the "magic bullet." This view was not shared by Gilman and colleagues who noted the variation in lymphomas and stated that it was unlikely that any compound would inhibit growth of all cancer cells [35].

Following the introduction of nitrogen mustard into clinical practice, other types of alkylating agents were developed many of which are in clinical practice today, most notably chlorambucil, melphalan, busufan, and cyclophosphamide [43].

Interestingly the clinical spectrum of their effectiveness is minimally changed from the initial report, although the toxicities differ.

The use of an antifolate compound was reported by Sidney Farber, initiating the development of antimetabolite therapy [44]. This was followed by the use of purine and pyrimidine analogs. Subsequently antitumor antibiotics, platinum compounds, imidizole compounds, vinca rosea alkaloids, taxols, camptothecin analogs, and biologic agents have become part of the therapeutic roster for neoplastic diseases [45].

The search for an anticancer agent that is selective for tumor, sparing normal tissues, continues to the present day. The vast increase in knowledge of biologic, genetic and molecular aspects of neoplastic disease has led to more specific forms of therapy including targeted forms of treatment, such as the anti-CD20 antibody for lymphoid malignancies and most recently STI 571 which is a specific inhibitor of the BCL-ABL fusion gene characterizing chronic myelogenous leukemia [46, 47]. The long-term effects of the newer targeted treatments had not been defined, but they are more specific and less toxic than conventional cytotoxic agents whose discovery led to the modern era of cancer treatment.

REFERENCES

1. *The Papyrus Ebers: The Greatest Egyptian Medical Document.* Ebbell, B., translator. Copenhagen: Levin and Munksgaard; 1937, pp. 110, 111, 124.
2. Breasted, J.H. Tumorous ulcers in the breast, perhaps resulting from injury. In: *The Edwin Smith Surgical Papyrus.* Chicago: University of Chicago Press; 1930, pp. 363-369.
3. Woelfer, A. Zur geschichte und operativen behandlung des zungenkrebses. Arch. fur Klin. Chir. 26:216, 1881.
4. Haagensen, C.D. An exhibit of important books, papers and memorabilia illustrating the evolution of the knowledge of cancer. Am. J. Cancer 135:42-51, 1933.
6. Dioscorides: Greek Herbal: Illustrated by a Byzantine A.D. 512. English translation by John Goodyear A.D. 1655. Edited and first printed A.D. 1933 by Robert T. Gunther. Oxford: Oxford University Press; 1934, pp. 43, 47, 77, 144, 198, 206, 208, 228, 238, 337, 465, 482, 491, 502, 642, 658.
6. Wolff, J. *The Science of Cancerous Diseases from Earliest Times to the Present.* Science History Publications; 1989. Originally published as Volume I. *Die Lehre bon der Krebshrankeit von den altestin Zeiten bis zeir Gegenwart.* Jena: Gastav Fischer; 1907. English translation by Barbara Ayaub; pp. 3.
7. *The Canon of Medicine of Avicenna.* Birmingham, Alabama: Classics of Medicine Library; 1984, pp. 447, 524.
8. Lissauer: Zwei Falle von Leucaeme. Berliner Klin. Wochnschr. 2: 403-404, 1865.
9. Cutler, E.G. and Bradford, E.H. Action of iron, cod-liver oil, and arsenic on the globular richness of the blood. Am. J. Med. Sci. 7574, 1878.
10. Forkner, C.E. The treatment of leukemia. In: *Leukemia and Allied Disorders.* New

York: The Macmillan Company; 1938, pp. 201-243.
11. Shen, Z.X., Chen, G.Q., Ni, J.H., Li, X.S., Xiong, S.M., Qiu, Q.Y., Zhu, J.P., Tang, W., Wun, G.L., Yang, K.Q., Chen, Y., Xhou, L., Fang, Z.W., Wang, Y.T., Ma, J., Zhang, P., Zhang, T.D., Chen, S.S., Chen, Z. and Wang, Z.Y. Use of arsenic Trioxide in the treatment of acute promyelocytic leukemia (APL). II. Clinical efficacy and pharmacokinetics in relapsed patients. Blood 89:3354-3360, 1997.
12. Soignet, S.L., Maslak, P., Wang, G., Jhanwar, S., Calleja, E., Dardashti, L.J., Corso, D., DeBlasio, A., Gabrilove, J., Scheinberg, D.A., Pandolfi, P.P. and Warrell, R.P., Jr. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. New Engl. J. Med. 339:1341-1348, 1998.
13. Kaplan, H.S. Historic milestones in radiobiology and radiation therapy. Semin. Oncol. 6:479-489, 1979.
14. Pusey, W.A. Report of cases treated with Roentgen rays. J. Am. Med. Assoc. 38:911, 1902.
15. Senn, N. Case of splenomedullary leukemia successfully treated by the use of Rontgen ray. M. Rec. 64:281, 1903.
16. Beatson, G.T. On the treatment of inoperable cases of carcinoma of the mamma: suggestions from a new method of treatment with illustrative cases. Lancet ii:104-107, 162-165, 1896.
17. Huggins, C.B., Stevens, R.E., Jr., and Hodges, C.V. Studies in prostatic cancer. II. The effect of castration on advanced carcinoma of the prostate gland. Arch. Surg. 4309-4323, 1941.
18. Hadow, A. Thoughts on chemical therapy. The David A. Karnofsky Memorial Lecture. Cancer 26:737-754, 1970.
19. Bainbridge, W.S. The Cancer Problem. New York: Macmillan; 1914, pp. 1-36, 108, 129, 237-276, 277-286.
20. Coley, W.B. Treatment of inoperable malignant tumors with toxins of erysipelas and the bacillus prodigious. Am. J. Med. Sci. 108:50-66, 1984.
21. Ewing, J. *The Parasitic Theory in Neoplastic Diseases*, 3rd edition. Philadelphia and London: W.B. Saunders Company; 1928, pp. 120-134.
22. Kellner, B. and Lustig, B. Beitrage zur chemischen Zusamensetzung von Mause-Impfcarcinomen sowie deren Beeinflussung durch verschiedenartige Ernahrung. Bioch. Zschr. 254:214-220, 1932.
23. Bryant, F. The treatment of cancer. Boston Med. Surg. J. 184:615-621, 1921.
24. Editorial: The treatment of cancer. Can. Practitioner Rev. 14:278-279, 1920.
25. Torrey, C. and Kahn, M.C. The treatment of Flexner-Jobling Rat carcinomas with bacterial proteolytic ferments. J. Cancer Res. 11: 334-376, 1927.
26. Strong, L.C. The establishment of the C3H strain of mice for the study of spontaneous carcinoma of the mammary gland. Genetics 20:586-591, 1935.
27. Zubrod, C.G., Schepartx, S., Leiter, J., Endicott, K.M., Cares, E.L.M., and Baker, C.G. the chemotherapy program of the National Cancer Institute: history, analysis and plans. Cancer Chemother. Rep. 50:349-350, 1966.
28. Krumbhaar, E.B. Role of the blood and the bone marrow in certain forms of gas poisoning. I. Peripheral blood changes and their significance. J. Am. Med. Assoc. 72: 39-41, 1919.
29. Krumbhaar, E.B. and Krumbhaar, H.D. The blood and bone marrow in yellow cross gas (mustard gas) poisoning. Changes produced in the bone marrow of fatal cases. J. Med. Res. 40:497-508, 1919.
30. Berenblum, I. and Riley-Smith. The modifying influence of dichloroethyl sulphide on the induction of tumours in mice by tar. J. Pathol. Bacteriol. 32:424-434, 1929.
31. Berenblum, I. and Riley-Smith. Experimental inhibition of tumour induction by mustard gas and other compounds J. Pathol. Bacteriol. 40:549-558, 1935.
32. Adair, F.E. and Bagg, H.J. Experimental and clinical studies on the treatment of cancer by dichlorethylsulphide (mustard gas). Am. J. Surg. 93:190-199, 1931.
33. Sipos, K. and Jasko, G. A mustarnirogen helyi alkamazasa nehany borbetegsagben. Borgyogyaszati es Venerologiciai Szemla 32:198-203, 1956.
34. Gilman, A. and Philips, F.S. The biological actions and therapeutic applications of the B-chloroethyl amines and sulfides. Science 103:409-415, 1946.
35. Gilman, A. The initial clinical trial of nitrogen mustard. Am. J. Surg. 105:574-578, 1961.
36. DeVita, V., Jr. In: Devita, V., Jr., Hellman, S., and Rosenberg, S.A., eds. *Cancer: Principles and Practice of Oncology.* Third edition. Philadelphia: Lippincott Company; 1993, pp. 276.
37. Donohower, R.C., Abeloff, M.D., and Perry, M.C. In: Abeloff, M.D., Armitage, J.O., Lichter, A.S., and Niederhuber, J.E., eds. *Chemotherapy in Clinical Oncology.* New York: Churchill Livingston; 1995, pp. 201.

38. Wilkinson, J.F. and Fletcher, R. Effect of β-chlorethylamine hydrochlorides in leukemia, Hodgkin's disease and polycythaemia vera: report on eighteen cases. Lancet ii:540-545, 1947.
39. Goodman, L.S., Wintrobe, M.M., Dameshek, W., Goodman, M.J., Gilman, A. and McLennan, M.T. Nitrogen mustard therapy. Use of methylbis(beta-chloroethyl) amine hydrochloride for Hodgkins disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. J. Am. Med. Assoc. 132:126-132, 1946.
40. Jacobson, L.O., Spurr, C.L., Barron, E.S.G., Smith, T., Lushbaugh, C. and Disk, G.F. Nitrogen mustard therapy. Studies on the effect of methyl-bis(beta-choroethyl) amine hydrochloride on neoplastic diseases and allied disorders of the hemopoietic system J. Am. Med. Assoc. 132:263-271, 1946.
41. Karnofsky, D.A., Craver, L.F., Rhodes, C.P., and Bels, J.C. An evaluation of methyl-bis(β-chloroethyl)amine hydrochloride and tris (β-chloroethyl) amine hydrochloride (nitrogen mustards) in the treatment of lymphomas, leukemia and allied diseases. In: *Approaches to Tumor Chemotherapy*. Washington, D.C.: American Association for the Advancement of Science; 1947, pp. 319-337.
42. Rhoads, C.P. Nitrogen mustards in the treatment of neoplastic disease. Official statement. J. Am. Med. Assoc. 131:656-658, 1946.
43. *Comparative Clinical and Biological Effects of Alkylating Agents*. Monograph of the New York Academy of Science; 1958.
44. Farber, S., Diamond, L.K., Mercer, Sylvester, R.F., Jr., and Wolff, J.A. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). N. Engl. J. Med. 238-787-793, 1948.
45. Burchenal, J.H. The historical development of cancer chemotherapy. Semin. Oncol. 4:135-146, 1977.
46. Czuczman, A.J., Grillo-Lopez-Grillo, C.A., White, M., Saleh, L., Gordon, A.F., LoBuglio, C., Jonas, D., Klippenstein, D., Dallaire, B., and Verns, C. Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. J. Clin. Oncol. 17:268-276, 1999.
47. Druker, B.J., Talpaz, M., Resta, D.J., Peng, B., Buchdunger, E., Ford, J.M., Lydon, N.B., Katarjian, H., Capdeville, R., Ohno-Jones, S. and Sawyers, C.L. Efficacy and safety of a specific inhibitor of the BCL-ABL tyrosine kinase in chronic myeloid leukemia. N. Engl. J. Med. 344:1031-1037, 2001.